

# **Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for 1,2-Dibromo-3-chloropropane (DBCP)**

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## **Office of Environmental Health Hazard Assessment (OEHHA) Reproductive and Cancer Hazard Assessment Section**

### **Summary**

The maximum allowable dose level (MADL) for 1,2-dibromo-3-chloropropane (DBCP) is **4.3 micrograms/day (µg/day)** by the inhalation route of exposure and **3.1 µg/day** by the oral route of exposure. These MADLs were derived based on the male reproductive effects observed in rabbits by Rao et al. (1982).

### **Background**

This report describes the derivation of a maximum allowable dose level (MADL) for 1,2-dibromo-3-chloropropane (DBCP) (CAS No. 96-12-8).

DBCP was used as a soil fumigant and nematocide, but is no longer manufactured commercially or used agriculturally in the U.S. However, extensive use of DBCP in the past has resulted in contamination of soil and underground aquifers in several areas of this country, in particular the Sacramento Valley of California (OEHHA, 1999). DBCP was listed under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as known to the State to cause reproductive toxicity (male reproductive toxicity), effective February 27, 1987. The Proposition 65 listing of DBCP was based on the statutory requirement that “such list shall include at a minimum those substances identified in Labor Code Section 6382(b)(1) and those substances identified additionally by reference in Labor Code Section 6382(d)” (Health and Safety Code section 25249.8(a)). Labor Code Section 6382(d) requires that “any substance within the scope of the federal Hazard Communication Standard (29 C.F.R. Sec. 1910.1200) is a hazardous substance subject to this chapter.” DBCP is recognized as a “Toxic and Hazardous Substance” by 29 C.F.R. Part 1910, Subpart Z and cited as an example for “reproductive toxins” in 29 C.F.R. Section 1910.1200, Appendix A (Health Hazard Definitions (29 C.F.R. Section 1910.1200) Appendix A (7)).

Procedures for the development of Proposition 65 MADLs are provided in regulations (Title 22, California Code of Regulations, §12801 and 12803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulations, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality (Title 22 Cal. Code of Regs. §12803).

## Study Selection

Relevant studies on the male reproductive toxicity of DBCP have been identified through literature searches. These studies, listed in the Bibliography for this document, have been reviewed and considered for the establishment of the MADL.

The male reproductive toxicity of DBCP has been clearly shown in numerous epidemiological studies in humans. However, exposure data in human studies are not adequate for a dose-response assessment and thus they cannot be used for identification of a NOEL.

The male reproductive toxicity of DBCP has also been extensively studied in laboratory animals. Major findings from several relevant animal studies that provided lowest observable effect levels (LOELs) and/or NOELs by inhalation or oral route of exposure are briefly summarized in Table 1. No reproductive study following dermal exposure that is of sufficient quality for the purpose of MADL development was found in the literature.

The NOEL is based on the most sensitive study deemed to be of sufficient quality (Title 22 Cal. Code of Regs. §12803 (a)(4)). Based on the findings from studies listed in the Table 1 and the discussions presented above, OEHHA determined that the rabbit study by Rao et al. (1982), is the most sensitive study of sufficient quality and consequently this study was used for establishment of the MADL for DBCP.

In the study by Rao et al. (1982), male New Zealand white rabbits six months of age (ten animals per group) were exposed by inhalation to 0, 0.1, 1.0 or 10.0 ppm of DBCP, six hours/day, and five days per week for a total of 14 weeks. The body weights of the animals were not reported. DBCP used in the study was 97.3% pure. In animals exposed to  $\geq 1$  ppm of DBCP, the authors found decreased testicular weights, apparent testicular atrophy, decreased sperm counts in semen ejaculates, and reduced mean number of implantations. Thus, the LOEL and NOEL for DBCP in this study are 1.0 and 0.1 ppm, respectively (Rao et al., 1982). These exposure levels are equivalent to 0.61 and 0.061 mg/kg-day, respectively, based on the calculations presented below.

**Table 1. Summary of the Male Reproductive Toxicity of DBCP**

<b>Study Reference</b>	<b>Animals</b>	<b>Treatment</b>	<b>General Toxicity</b>	<b>Reproductive Effects &amp; LOEL</b>	<b>NOEL (adjusted)</b>
Rao et al., 1982	Male New Zealand White rabbits, 10/group	<b>Inhalation</b> , 0, 0.1, 1.0, 10 ppm, 6 h/d, 5 d/wk for 14 wks	High mortality at 10 ppm; No other sign of general toxicity.	Decreased testis weights and sperm counts; testicular atrophy; increased serum FSH. LOEL=1.0 ppm (0.61 mg/kg-day)	0.1 ppm (0.061 mg/kg-day)
Rao et al., 1983	Sprague-Dawley rats, male, total of 30 rats per group.	<b>Inhalation</b> , 0, 0.1, 1.0, 10 ppm. 6 h/d, 5 d/wk for 14 weeks	No overt clinical sign of toxicity or change in body weight gain.	Decreased testis weights; testicular atrophy; increased post-implantation loss. LOEL= 1.0 ppm (0.95 mg/kg-day)	0.1 ppm (0.10 mg/kg-day)
Foot et al., 1986a; 1986b	Dutch rabbits, male, 6/group	<b>Drinking water</b> , 0, 0.94, 1.88, 3.75, 7.5, 15 mg/kg, 5 d/wk, 10wks	No effect on body weight gain. No obvious general toxicity.	Decreased testis weights, epididymal sperm counts, and germ cell numbers. LOEL= 1.88 mg/kg	0.94 mg/kg (0.64 mg/kg-day)
Heindel et al., 1989	Sprague-Dawley rats, male, 20/group	<b>Drinking water</b> , 0, 5, 50, 100, 200 ppm for 64 days	Decreased body weight gain and water consumption.	Decreased testis weights; no effect on testicular morphology. LOEL= 200 ppm.	100 ppm (5.4 mg/kg-day)
Amann & Berndtson, 1986	Sprague-Dawley rats, male, 15/group	<b>Gavage</b> , 0, 0.94, 1.88, 3.75, 7.5, 15 mg/kg/d for 77 days	Decreased body weight gain at 15 mg/kg/d.	Decreased testis weights & sperm counts. LOEL= 15 mg/kg-day	7.5 mg/kg-day
Ahmad et al., 1988	Long-Evans rats, male, 6-30 per group	<b>Gavage</b> , 1, 5, 25 mg/kg/d for up to six months.	Decreased body weights at 5 and 25.	Decreased testis weights; germ cell death. LOEL= 5 mg/kg-day	1 mg/kg-day
Johnston et al., 1986	Sprague-Dawley rats, one-generation reproduction study	<b>Drinking water</b> , 0, 0.02, 0.2, 2.0, 20 mg/kg/d; males and females were exposed.	Decreased body weight gains at 20 mg/kg-day.	Decreased average litter weight of pups at the highest dose; no effect on testis weights or morphology.	20 mg/kg-day (14.47 mg/kg-day estimated by the authors)
Chapin & Sloane, 1997	CD-1 mice, two-generation reproduction study	<b>Gavage</b> , 0, 25, 50, 100 mg/kg, both males and females in two generations were exposed	No effect in body weight gains; increased relative liver weight in F1 male adults at 100 mg/kg	Decreased relative epididymis and prostate weights in F1 male adults at 100 mg/kg. LOEL =100 mg/kg-day	50 mg/kg-day

**Notes:** 1. Adjusted NOEL: NOELs reported in the original reports were adjusted to mg/kg-day following the methods described in the "MADL Calculation" section of this document.

2. Inhalation rate (IR) for rabbits was derived from body weights (W):  $IR (m^3/day) = 0.46 \cdot W^{0.8307}$ ; U.S. EPA, 1988). For rats, the method by Anderson et al. was used:  $IR (m^3/day) = 0.105 [W/0.113]^{2/3}$ , (Anderson et al., 1983).

## MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day. The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL ((Title 22 Cal. Code of Regs. §12803). For male reproductive toxicity, the assumed body weight of a man is 70 kg.

The following calculations were performed to derive the MADL for DBCP via inhalation, based on a NOEL of 0.1 ppm found in the rabbit study by Rao et al. (1982):

Conversion of air concentration in ppm to mg/m<sup>3</sup> using a conversion factor of 9.67 (OEHHA, 1999):

$$0.1 \text{ ppm} \times 9.67 = 0.97 \text{ mg/m}^3$$

Adjusting for purity (97.3%):

$$0.97 \text{ mg/m}^3 \times 97.3\% = 0.94 \text{ mg/m}^3$$

Calculation of NOEL expressed as mg/kg-day, based on a body weight of 3.73 kg for six-month-old male New Zealand white rabbits with an inhalation rate of 0.057 m<sup>3</sup>/hr (see footnote 2 to Table 1):

$$(0.94 \text{ mg/m}^3 \times 0.057 \text{ m}^3/\text{hr} \times 6 \text{ hr/day}) \div (3.73 \text{ kg}) = 0.086 \text{ mg/kg-day}$$

Conversion from five days/week to seven days/week:

$$0.086 \text{ mg/kg-day} \times (5 \text{ days} \div 7 \text{ days}) = 0.061 \text{ mg/kg-day}$$

Calculation of NOEL for a 70 kg man:

$$0.061 \text{ mg/kg-day} \times 70 \text{ kg} = 4.27 \text{ mg/day}$$

The MADL is derived by dividing the NOEL by one thousand ((Title 22, Cal. Code of Regs., § 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

$$\text{MADL}_{\text{inhalation}} = 4.27 \text{ mg/day} \div 1000 = 4.27 \text{ } \mu\text{g/day}, \text{ or } \mathbf{4.3 \text{ } \mu\text{g/day}} \text{ after rounding.}$$

This MADL represents intake by the inhalation route of exposure. Approximately 50% of an administered dose of DBCP is absorbed via the inhalation route of exposure (Gingell et al., 1987; OEHHA, 1999). The MADL for DBCP via the inhalation route of exposure as proposed above is thus equivalent to an absorbed dose of approximately 2.2 μg/day (4.3 μg/day × 50%).

In addition to the inhalation route of exposure, exposure of humans to DBCP can also occur via oral, dermal, or multiple routes of exposure. Approximately 70% (68-78%) of DBCP is absorbed in rats following oral administration (OEHHA, 1999). The absorbed

dose of 2.2 µg/day is thus equivalent to an intake of 3.1 µg/day following oral route of exposure ( $2.2 \mu\text{g/day} \div 70\% = 3.1 \mu\text{g/day}$ ). For the purposes of Proposition 65, the MADL for DBCP via the oral route of exposure is 3.1 µg/day.

If exposures occur by dermal or multiple routes, the total exposure to the chemical from a single source or product must be considered. The absorbed dose resulting from any one or multiple routes of exposure should be calculated. If the total absorbed dose resulting from any one or multiple routes is less than or equal to 2.2 µg/day, the MADL has not been exceeded.

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